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EXAMINER

GODDARD, LAURA B

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 05/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/687,035	Applicant(s) ALBONE ET AL.	
	Examiner Laura B. Goddard, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 March 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-119 is/are pending in the application.
- 4a) Of the above claim(s) 29-31, 33-37, 39-43, 45-48, 78-102 and 113-115 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-28, 32, 38, 44, 49-77, 103-112 and 116-119 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 9/8/04, 11/29/04, 12/15/04, 5/18/05
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. The Election filed March 6, 2006 in response to the Office Action of January 11, 2006 is acknowledged. Applicant elected with traverse Group I, and the species of antibody and hybridoma 776.1 and SEQ ID NOs:33 and 34 which are drawn to claims 1-26, 28, 32, 38, 44, 49-77, 103-112, 116, 118, and 119.

Upon further review and consideration, Examiner has rejoined Groups I and II. Group II is drawn to claims 27 and 117, a monoclonal antibody that competes with binding of antibody 776.1.

Claims 1-119 are pending. Claims 29-31, 33-37, 39-43, 45-48, 78-102, and 113-115 are withdrawn from further consideration by the examiner under 35 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1-28, 32, 38, 44, 49-77, 103-112, and 116-119 are currently under prosecution.

Specification

2. The disclosure is objected to because of the following informalities: There appears to be an error on pages 7, 8, 32, and 33. On page 8 and 33, SEQ ID NO:33 should be associated with (776.1L), not (16H9L) which appears to be the wrong antibody. On page 7 and 32, ("16H9") should be ("16H9H") to correctly describe the heavy chain variable region of 16H9 antibody. Appropriate correction is required.

Claim Objections

3. Claims 2-6, 12, 49-53, and 119 are objected to because they recite "Figure 1".

Examiner suggests replacing "Figure 1" with **SEQ ID NO:1** to better clarify the peptide reference.

4. Claims 56-60 are objected to because they recite the acronym "ADCC" in reference to an assay. Examiner suggests defining the acronym ADCC as **antibody-dependent cellular cytotoxicity** to clarify the type of assay (see p. 3, [0014], of the specification).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claim 117 is rejected under 35 U.S.C. 101 because the claimed invention, an antibody, is directed to non-statutory subject matter.

The claims read on an antibody that is found in nature. Products of nature do not constitute patentable subject matter as defined in 35 USC 101. See MPEP 2105. Since an antibody does not exist in nature in purified form, it is suggested that Applicant use the language "isolated" or "purified" in connection with the antibody to identify a product that is found in nature.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-25, 49-76, 103-106, and 110-112 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The use of laboratory designations only to identify a particular polypeptide such as "cell-associated CA 125/O772P" or "shed CA 125/O772P" renders the claims indefinite because different laboratories may use the same laboratory designation to define completely distinct proteins or protein fragments. WO 00/36107, Mitcham et al, published 6/22/2000 teach that there are several different sequences for different forms of the CA 125/O772P polypeptide (p. 52, lines 11 and 13). The specification identifies different CA 125/O772P polypeptides such as, CA 125/O772P 3-repeat, also identified as SEQ ID NO:1, and CA 125/O772P 3-repeat TM, also identified as SEQ ID NO:2, (p. 22 and 23, Figs 1 and 2), and it is unclear in the claim how the polypeptides are structurally different because they share the same polypeptide name with only the adjectives "shed" and "cell-associated" distinguishing them. The specification does not provide a nexus between the adjectives "shed" and "cell-associated" with a SEQ ID NO or distinguishing structures between the two types of CA 125/O772P polypeptides, hence it is unclear what a "shed" versus a "cell-associated" CA 125/O772P polypeptide is. It is also unclear if the sequence in Fig.1 is the shed or cell-associated CA 125/O772P polypeptide since the claims only refer to it as "the peptide of Fig. 1". Amendment of the claims, for example, to include

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the **SEQ ID numbers** which unambiguously defines the CA 125/O772P polypeptides, or to include **the deposited antibodies** that distinguish between binding preferences to the shed and cell-associated polypeptide, would obviate the rejection.

7. Claims 49-53 contain the trademark/trade names **BIAcore Affinity Assay**.

Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe an antigen-antibody affinity assay, accordingly, the identification/description is indefinite, MPEP 7.35.01.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 26-28, 107-109, and 116-118 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s)

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contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to an antibody or hybridoma that produces antibody 325.1, 621.1, 633.1, 654.1... 776.1 or an antibody that competes with binding of said antibody. Since the antibody is essential to the claimed invention it must be obtainable by a repeatable method set forth in the specification or otherwise readily available, the requirements of 35 USC 112 may not be satisfied by a deposit of the antibody or antigen to which it binds. The specification does not disclose a repeatable process to obtain the antibody and it is not apparent if the antibody is readily available to the public. It is noted that the specification discloses deposits of the hybridomas with the ATCC under the Budapest Treaty on pages 101-104. When the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that **the specific antibody will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required,** would satisfy the deposit requirement made herein.

9. Claims 1-25, 49-76, 103-106, and 110-112 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a WRITTEN DESCRIPTION rejection.

The claim is drawn to an isolated antibody, or an antigen-binding fragment, that preferentially binds cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide (claim 1, 13-25, 104-106), wherein the antibody exhibits less than a specified percent inhibition of binding to the peptide of Fig. 1 (SEQ ID NO:1) in the presence of a 25-fold (weight/weight) excess of shed CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide over the peptide of Fig. 1 in an ELISA competition assay (claims 2-6) wherein the antibody exhibits an IC_{50} as measured by a specified mg/ml shed CA 125/O772P polypeptide (claims 7-11), wherein the antibody binds the peptide of Fig. 1 (SEQ DI NO:1) but does not bind detectable shed CA 125/O772P polypeptide (claim 12), wherein the antibody binds the peptide of Fig. 1 with a K_d of less than about a specified nM amount as measured in a BIAcore Affinity Assay (claims 49-53), wherein the antibody is modified by amino acid substitution, deletion, or addition, or a combination thereof and has the same or increased affinity for cell-associated CA 125/O772P relative to that of a corresponding unmodified antibody (claim 54), wherein the antibody is modified by amino acid substitution, deletion, or addition, or a combination thereof and exhibits the same or an increased serum half-life compared to that of a corresponding unmodified antibody (claim 55), the antibody of claim 1 wherein the antibody mediates lysis of CA 125/O772P-positive tumor cells in an ADCC assay (claims 56-60), the antibody of claim 1 wherein the antibody mediates lysis

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of CA 125/O772P-positive tumor cell in a CDC assay (claims 61 and 62), the antibody of claim 1 wherein the antibody inhibits CA 125/O772P-positive tumor growth (claim 63), a pharmaceutical composition comprising an antibody or antibody fragment that preferentially binds cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide (claims 64-76, 110-112), a fusion polypeptide comprising an antibody that preferentially binds cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide operably linked to a heterologous agent (claim 77), and a hybridoma that can secrete the antibody of claim 1 (claim 103).

The specification discloses antibodies in Tables 7 and 8, page 83 that are specific for CA 125/O772P polypeptide (SEQ ID NO:1) (p. 82). The specification discloses antibodies in Table 11 and 12 that preferentially bind cell-associated CA 125/O772P polypeptide (p. 87-88). A flow cytometry competition assay identified antibodies that preferentially bind to cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide (p. 88-89, Tables 13 and 10). A BIAcore affinity assay identified antibodies that bind with high affinity to CA 125/O772P polypeptide (p. 90, Table 14). An ADCC assay identified antibody 117.1 as capable of mediating lysis of ovarian cancer cells in a dose-dependent manner (p. 91-92; Fig. 4). The specification discloses the sequences of antibodies that preferentially bind cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide (p. 6-8; Figs. 5A-10D; p. 92-94) and the hybridomas producing said antibodies (p. 9). The specification discloses SEQ ID NO:1 and 2 as sequences of a CA 125/O772P polypeptide.

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To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of "preferentially binds cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide", "modified by amino acid substitution, deletion, or addition, or a combination thereof", "has the same or increased affinity for cell-associated CA 125/O772P relative to that of a corresponding unmodified antibody", "exhibits the same or an increased serum half-life compared to that of a corresponding unmodified antibody", "inhibits CA 125/O772P-positive tumor growth", or a binding characteristic determined by an ELISA competition assay, flow cytometry competition assay, affinity assay, or mediation of cell lysis as determined by ADCC assay, or CDC assay. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The

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court stated that " [a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it from other materials. " *Id.* At 1567, 43 USPQ2d at 1405. The court also stated that:

a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-

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Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that “the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristicsi.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.” Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. Thus, the instant specification may provide an adequate written description the claimed antibody, hybridoma, and pharmaceutical composition, per Lilly by structurally describing representative shed and cell-associated CA 125/O772P polypeptides or by describing specific antibodies with the claimed characteristics as stated above or by describing “structural features common to the members of the genus, which features constitute a substantial portion of the genus.” Alternatively, per Enzo, the specification can show that the claimed invention is complete “by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.”

In this case, the specification does not directly describe a shed and cell-associated CA 125/O772P polypeptide, or antibodies that preferentially bind to cell-

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associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide, or antibodies with modifications or any other claimed characteristics or functions stated above useful in the claimed invention in a manner that satisfies either the Lilly or Enzo standards. There are no distinguishing structural characteristics described to differentiate cell-associated from shed CA 125/O772P polypeptide, hence the Applicant does not have possession of the genus of antibodies that preferentially bind one polypeptide and not the other. There are no structural features associated with the various claimed functions and characteristics of the antibodies. The specification describes deposited antibodies and sequences of antibodies that preferentially bind cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide, these antibodies provide structural features associated with the claimed function of preferentially binding cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide. Although the specification discloses SEQ ID NO:1 and 2, this does not provide a description of the broadly claimed cell-associated and shed CA 125/O772P polypeptides that would satisfy the standard set out in Enzo because the specification provides no functional characteristics coupled to structural features.

Further, the specification also fails to describe antibodies that that preferentially bind cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide or have some of the claimed characteristics as stated above, by the test set out in Lilly because the specification describes only SEQ ID NO:1 and 2 and deposited antibodies that preferentially bind cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide. Therefore it necessarily fails to describe a

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representative number of such species of cell-associated and shed CA 125/O772P or antibodies that preferentially bind to cell-associated CA 125/O772P or have specific functions or characteristics as stated above.

Thus, the specification does not provide an adequate written description of a shed or and cell-associated CA 125/O772P polypeptide, or antibodies that preferentially bind to cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide, or antibodies with modifications or any other claimed characteristics or functions stated above that is required to practice the claimed invention. Amendment of the claims, for example, to incorporate SEQ ID NOs to define the shed and cell-associated CA 125/O772P polypeptides, or to incorporate the deposited antibody into the claims may obviate the rejection.

10. Claims 63-76, 110-112, and 118 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized in *re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The court in *Wands* states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to

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practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to an isolated antibody of claim 1 wherein the antibody inhibits CA 125/O772P-positive tumor growth (claim 63), a pharmaceutical composition comprising an antibody or monoclonal antibody that preferentially binds cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide (64-76 and 118), wherein the antibody is conjugated to a cytotoxic agent (claims 110-112).

The specification discloses that radiolabeled antibody [¹³¹I] 776.1 successfully slows tumor growth in mice wherein the mice were implanted with subcutaneous tumors expressing CA 125/O772P antigen (p. 96-99). The specification discloses that antibodies that preferentially bind cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide can be utilized to prevent, manage, or ameliorate

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125/O772P-related disorders or symptoms of the disorder, for example, cancer, e.g. ovarian cancer (p. 26, [0114]).

One cannot extrapolate the teaching of the specification to the enablement of the claims because the specification does not provide guidance or working examples for an antibody that preferentially binds cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide and **inhibits CA 125/O772P-positive tumor growth or a pharmaceutical** comprising an antibody that preferentially binds cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide. The specification discloses only *in vivo* treatment of subcutaneous ovarian tumors expressing CA 125/O772P polypeptide upon subsequent administration of antibody 776.1 (an antibody that preferentially binds cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide) that was attached to a radioactive label. Clearly, antibody 776.1 provides a means for targeting the CA 125/O772P ovarian cancer antigen to deliver cytotoxic agents, such as a radioactive label, to ovarian cancer cells expressing CA 125/O772P. However, it is not clear that the antibody can slow or treat tumor growth alone. The term "pharmaceutical" is defined as a pharmaceutical product or preparation (American Heritage Dictionary of the English Language, 4th Ed., 2000, p. 1) or relating to drugs: involved in or related to the manufacture, preparation, dispensing, or sale of drugs used in medicine (MSN Encarta, Dictionary, p. 1). The term "pharmaceutical" defines the antibody composition as a drug composition with the purposes of treating 125/O772P-related disorders such as ovarian cancer, as disclosed in the specification (p. 26, [0114]). The specification does not provide guidance or

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working examples for the treatment of ovarian cancer expressing CA 125/O772P polypeptide by administration of the antibody alone, meaning without a cytotoxic agent attached to the antibody.

Further, Berger et al (Cancer Biotherapy & Radiopharmaceuticals, 2005, 20:589-602) teach that antibody 776.1 may be a promising radioimmunotherapeutic for the treatment of human ovarian cancer. Berger et al teach that Yttrium-labeled 776.1 antibody ([⁹⁰Y-DOTA]776.1) slowed tumor growth for subcutaneous ovarian tumors in mice (p. 599 and Fig. 5), however, Berger et al teach that in the subcutaneous model, shed CA 125 is not present at significant levels in the serum of the mice, and thus it is not known if 776.1 still can target the tumor *in vivo* in the presence of clinically relevant concentrations of CA 125 (p. 600, col. 1). Berger et al provide data that unlabeled 776.1 antibody was unable to significantly slow tumor growth (Table 3 and Figure 5). Given the lack of guidance and example in the specification and the teaching of Berger et al, one of skill in the art could not use 776.1 or 776.1 attached to a cytotoxic agent as a pharmaceutical or to inhibit CA 125/O772P-positive growth because 776.1 alone has no significant effects on the treatment of ovarian tumors, and the presence of shed CA 125/O772P polypeptides in the serum of ovarian cancer patients in a clinical setting may inhibit the binding of 776.1 to the cell-associated CA 125/O772P polypeptide because ovarian cancer is not a subcutaneous tumor. A search of the prior art does not teach or enable the claimed antibody that preferentially binds cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide that would function as a pharmaceutical or slow ovarian tumor growth in a clinical setting.

Finally, the specification does not provide guidance or examples for **preventing or treating *any*** cancer, 125/O772P-related disorder, and cell proliferative disorder as claimed. Clearly, any cancer or any disorder that does not comprise tumor tissue expressing 125/O772P antigen, would not be treated by the administration of an antibody that binds to the antigen because the antigen is not expressed. Regarding the prevention of cancer, 125/O772P-related disorder, or a cell proliferative disorder, the specification lacks the critical steps necessary in presenting some type of predictable response in a population of hosts deemed necessary to prevent cancer. Reasonable guidance with respect to preventing any cancer, 125/O772P-related disorder, or cell proliferative disorder relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of cancer or have had cancer. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and link those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease. All of this underscores the criticality of providing workable examples which are not disclosed in the specification.

The specification provides insufficient guidance with regard to these issues, and it cannot be reasonably predicted that a composition comprising an antibody that preferentially binds cell-associated CA 125/O772P polypeptide relative to shed CA

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125/O772P polypeptide or said antibody attached to a cytotoxic agent would inhibit CA 125/O772P-positive tumor growth or would predictably function as a pharmaceutical as claimed. Therefore, in view of the novel nature of the invention, the state of the art, the lack of guidance in the specification, and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

11. Claims 25, 32, and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for **an antibody that preferentially binds cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide and comprises both a heavy and light chain variable region with all corresponding 6 complementarity-determining regions (CDRs)**, does not reasonably provide enablement for an antibody with a single light or single heavy chain variable region or an antibody that does not contain all 6 corresponding CDRs that comprise the binding site for binding to cell-associated CA 125/O772P polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). The court in *Wands* states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to

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practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to an antibody that preferentially binds cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide, wherein the antibody is a VL-containing fragment, VH-containing fragment, CDR-containing fragment (claim 25), wherein the antibody comprises a light chain variable region comprising SEQ ID NO:33 (claims 32), wherein the antibody comprises a heavy chain variable region that comprises SEQ DI NO:34 (claim 38). The claims are drawn to antibodies that contain a single CDR or a single heavy or single light chain variable region, as opposed to a whole, complete antibody or antibody or antibody fragment comprising both corresponding heavy and single light chain variable regions that form the binding site to the CA 125/O772P polypeptide.

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The specification discloses the heavy and light variable chain sequences that correspond to the binding site of specific antibodies that preferentially bind cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide (p. 6-8; Figs. 5A-10D). The specification discloses that antibodies that preferentially bind cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide can be utilized to prevent, manage, or ameliorate 125/O772P-related disorders or symptoms of the disorder, for example, cancer, e.g. ovarian cancer (p. 26, [0114]). The specification discloses that such antibodies and antigen-binding fragments are useful for a variety of therapeutic, prophylactic, diagnostic, and purification purposes (p. 27, [0116]). The specification discloses that said antibodies bind SEQ ID NO:1 or 2 (p. 2, [0010]; p. 3; p. 27, [0117]).

One cannot extrapolate the teaching of the specification to the scope of the claims because the specification does not provide examples or guidance for making an **antibody that comprises a single CDR, single heavy or single light chain variable region** that would function as claimed and contemplated. Janeway et al (Immunobiology, 2001, 5th Ed., Garland Publishing, New York) teach that when the V_L and V_H regions are paired in an antibody molecule, the hypervariable loops from each domain are brought together, creating a single hypervariable site at the tip of each arm of the molecule. The three hypervariable loops determine antigen specificity by forming a surface complementary to the antigen, and are more commonly termed the complementarity-determining regions, or CDRs (CDR1, CDR2, and CDR3). Because CDRs from both V_L and V_H regions contribute to the antigen-binding site, it is the

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combination of the heavy and light chain, and not either alone, that determines the final antigen binding specificity (section 3-6). The surface of the antibody molecule formed by the juxtaposition of the CDRs of the heavy and light chains creates the site to which an antigen binds. Clearly, as the amino acid sequences of the CDRs are different in different antibodies, so are the shapes and surfaces created by these CDRs (section 3-7). Given the required participation of hypervariable regions of both the light and heavy chains of an antibody and the interaction between the V_L and V_H CDRs necessary to form a specific antigen-binding site, one of skill in the art could not make an antibody comprising a single CDR or a single heavy or light chain of an antibody that would predictably bind to CA 125/O772P polypeptide (SEQ ID NO:1 or 2) or preferentially bind cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide.

The specification discloses only specific SEQ ID NOs of heavy and light chain variable regions that correspond to specific monoclonal antibodies that preferentially bind cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide, such as SEQ ID NO:33 and 34 for antibody 776.1. The art teaches that minor changes in the amino acid sequence of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function (Rudikoff et al, PNAS, USA, 1982, 79: 1979). Rudikoff et al teach that alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein results in the loss of antigen-binding function. Janeway et al, above, teach as the amino acid sequences of the CDRs are different in different antibodies, so are the shapes and surfaces created by these CDRs (section 3-7) and it is the surface of the antibody molecule formed by the

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juxtaposition of the CDRs of the heavy and light chains that creates the site to which an antigen binds. Clearly, *any* antibody or antibody fragment that comprises a single CDR or single hypervariable region and lacks the corresponding CDRs or hypervariable regions, or is paired with CDRs or variable regions from different antibodies would not predictably preferentially bind cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide and function as claimed and contemplated.

A search of the prior art does not teach or enable the claimed antibody that preferentially bind cell-associated CA 125/O772P polypeptide relative to shed CA 125/O772P polypeptide wherein the antibodies or antibody fragments comprise a single CDR, single heavy, or single light chain variable region.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be reasonably predicted that antibodies or antibody fragments that comprise a single CDR, single heavy, or single light chain variable region, will predictably function as claimed and contemplated. Therefore, in view of the novel nature of the invention, the state of the art, the breadth of the claims, lack of guidance in the specification, and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claim 119 is rejected under 35 U.S.C. 102(b) as being anticipated by Yin and Lloyd, Journal of Biological Chemistry, July 2001, 276:27371-27375 (see sequence search result #1 in the UnitProt database).

The claim is drawn to an isolated antibody or antigen-binding fragment that binds to the peptide of Figure 1 (SEQ ID NO:1).

Yin and Lloyd teach antibodies that bind to CA125 ovarian cancer antigen (p. 27371, col. 2; Fig. 3; p. 27375, col. 1). The CA125 antigen shares 92.9% homology and 99.9% local similarity with the polypeptide depicted in Fig. 1 (SEQ ID NO:1, CA125/O772P) of the instant application (see sequence search result #1 in the UnitProt database). It would be expected that a subset of antibodies that bind to the CA125 antigen taught by Yin and Lloyd would also bind to the polypeptide of Fig. 1 in the instant application, hence, all the limitations of the claims are met.

13. Claim 119 is rejected under 35 U.S.C. 102(b) as being anticipated by WO 00/36107, Mitcham et al, published 6/22/2000 (see sequence search result #3 in the Geneseq database).

The claim is drawn to an isolated antibody or antigen-binding fragment that binds to the peptide of Figure 1 (SEQ ID NO:1).

WO 00/36107 teaches an ovarian carcinoma O772P polypeptide SEQ ID NO:389 (encoded by polynucleotide SEQ ID NO:386) and antibodies that bind to said polypeptide (p. 2, lines 14-24; p. 21-24; p. 50, lines 1-5; p. 52, line 13). The ovarian

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carcinoma O772P polypeptide SEQ ID NO:389 shares 92.9% homology and 99.9% local similarity with the polypeptide depicted in Fig. 1 (SEQ ID NO:1, CA125/ O772P) of the instant application (see sequence search result #3 in the Geneseq database). It would be expected that a subset of antibodies that bind to the CA125 antigen taught by WO 00/36107 would also bind to the polypeptide of Fig. 1 in the instant application, hence, all the limitations of the claims are met.

14. **Conclusion:** No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Laura B Goddard, Ph.D.
Examiner
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JEFFREY SIEW
SUPERVISORY PATENT EXAMINER